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**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**

EISAI CO., LTD. and EISAI INC.,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., and GATE PHARMACEUTICALS (a division of Teva Pharmaceuticals USA, Inc.),

Defendants.

Consolidated
Civil Action Nos.

05-cv-5727 (HAA) (ES)
07-cv-5489 (HAA) (ES)

**MEMORANDUM OF LAW**
**IN SUPPORT OF**
**PLAINTIFFS' MOTION FOR A PRELIMINARY INJUNCTION**

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## PRELIMINARY STATEMENT

This is a Hatch-Waxman patent infringement suit. Defendants Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc.'s ("Teva") filed two Abbreviated New Drug Applications ("ANDAs") with the Food and Drug Administration ("FDA"), seeking approval to market a generic version of Plaintiffs Eisai Co., Ltd. and Eisai Inc.'s ("Eisai") flagship drug for the treatment of Alzheimer's disease, Aricept®. Eisai has sued Teva for infringement of Eisai's basic compound patent, U.S. Patent No. 4,895,841 ("the '841 patent"), covering the active ingredient in Aricept®, a compound known as donepezil. Donepezil was a pioneering discovery, winning the pharmaceutical equivalent of the Nobel Prize.

Many generic drug companies have filed ANDAs with "Paragraph III" certifications respecting the '841 patent. Under the Hatch-Waxman Act, this means that they are content to wait until the '841 patent expires in November 2010 before selling generic donepezil. Teva itself has long acquiesced in the '841 patent. In 1996, Teva wrote Eisai seeking rights in donepezil. By 1997, Teva admits that it knew of the '841 patent. In October 2004, after consulting outside patent counsel, Teva filed an ANDA with a Paragraph III certification acquiescing in the validity of the '841 patent. In the summer of 2005, Teva again asked Eisai for rights in Aricept®, threatening a patent challenge if Eisai did not cooperate.

Nevertheless, Eisai declined. So, in October 2005, consistent with its threat, Teva filed a Paragraph IV certification attacking the '841 patent as being invalid for obviousness. In December 2006, Teva completely changed its obviousness theory. Then, near the end of 2007, Teva conceded the '841 patent satisfies the criteria for patentability and jettisoned its obviousness defense. In its place, Teva asserted a new inequitable conduct defense modeled on a defense that Teva had just lost in a case between the parties in the Southern District of New York.

Under the Hatch-Waxman Act, 21 U.S.C. § 355(j), when Eisai sued Teva for infringement, 30-month stays were triggered during which the FDA could not approve Teva's applications. The stay on Teva's ANDA ends on April 28, 2008, after which the FDA may immediately approve that application. Teva has announced that it intends to launch its generic product "at-risk" after the 30-month stay ends. Because the premature launch by Teva will have an immediate, devastating and irreparable impact on Eisai's business -- which cannot be remedied even by Eisai's subsequent win at trial -- Eisai has no choice but to bring this motion for a preliminary injunction.

It is hard to conceive a more compelling case of irreparable harm than presented by Eisai in this motion. Aricept® is a blockbuster drug, experiencing double-digit growth in sales every year it has been on the market, in a testament to its wide and ever growing use among physicians. Sales are continuing to grow

even in the last years of life of the patent. Aricept® is one of the two major drugs sold by Eisai in the United States. Eisai depends critically on the substantial revenue from the sales of Aricept®, particularly in this last remaining window of patent life. Aricept® sales provide over 70% of plaintiff Eisai Inc.'s profits.

Given Eisai's dependence on this revenue, the sudden loss from Teva's generic launch will cause a cascade of irreparable harms, including the effective end of Eisai's remaining patent term, firing of personnel in New Jersey and elsewhere, and the inability to fund critical research programs necessary for the continued operation of the company.

Eisai will succeed on the merits. *Teva has stipulated to infringement.* (Docket # 109.) Eisai thus has no burden of proof at trial. *Teva has conceded patent validity.* (Docket # 112, ¶ 7.) Eisai has therefore already succeeded on the defense that prompted this lawsuit at its outset.

Teva's newly-raised defense of inequitable conduct is precisely the sort of "last-resort" allegation condemned by the Federal Circuit as a plague on the patent system. Teva's defense will not withstand more than superficial scrutiny. Teva argues materiality of two items of information not considered by the '841 patent examiner: (1) a prior patent by Eisai (U.S. Patent No. 4,849,431) claiming compounds which are structurally distinct from the compounds claimed in the '841 patent (the basic core structures of the molecules have entirely different left sides);

and (2) a generalized sketch in an article about antidotes for chemical warfare agents that illustrates two theoretical binding "regions" of the acetylcholinesterase enzyme.[1] To assert materiality, Teva combines this information with a patent considered by the '841 patent examiner (Paragamian, U.S. Patent No. 3,476,759).

In particular, Teva says the '431 patent was material because it would have been used for an "obviousness-type double patenting" rejection of certain claims of the '841 patent. Teva argues that a person of ordinary skill and the examiner, based on the sketch, would have combined one half of the core structure of the '431 patent claims with a piece of a chemical used in Paragamian as an intermediate to make a different compound having an entirely different function (treatment of hypertension), and reasonably expected this mix-and-match molecule to be effective at treating Alzheimer's disease.

Every step of Teva's argument is fundamentally defective. Teva's argument conflicts with basic science, the references Teva cites and Eisai's internal data. Teva relies on improper hindsight to propose arbitrary changes to chemical structures and then assert that these major changes in this highly unpredictable field would have been "reasonably expected" to result in an effective Alzheimer's disease drug. Teva's argument also conflicts with the patent prosecution histories

[1] Kenley *et al.*, "Nonquaternary Cholinesterase Reactivators. 2. α-Heteroaromatic Aldoximes and Thiohydroximates as Reactivators of Ethyl Methylphosphonyl-Acetylcholinesterase *in Vitro*." J. Med. Chem. 27:1201-11 (1984) ("Kenley").

themselves and basic patent office practice and procedure, which demonstrate that neither a reasonable examiner nor a person of ordinary skill would make the combination proposed by Teva and that no disclosure was required under the Manual of Patent Examining Procedure.

Teva cannot and will not prove intent to deceive. Teva misstates the work done by Eisai and offers speculation and improper inferences-on-inferences-on-inferences. The equities clearly favor maintaining the patent on the remarkable invention of Aricept®.

Teva does not even assert that the non-disclosed information would have been material to the '841 patent claim specific to donepezil -- the compound Eisai cared about. Teva's meritless inequitable conduct argument thus asks the Court to accept the premise that Eisai concealed information, jeopardizing its patent application on the important discovery of donepezil, when this information was not even relevant to the patentability of donepezil. Teva also asks the Court to believe that Teva's information is highly material to patentability because it would have resulted in double-patenting rejections, yet Teva never even raised double-patenting when seeking to attack the validity of the '841 patent. With the prospect of stealing away Eisai's billion-plus dollar a year business, if Teva's argument had even a whiff of credibility, Teva would have tried to raise double patenting as an invalidity defense. Teva never made that argument and now concedes validity.

Aricept® is the epitome of a scientific advance intended to be rewarded by the United States patent system. Aricept® was the very first practical treatment approved by the FDA for Alzheimer's disease, and is still the most widely used treatment over eleven years later. Teva should be ordered to continue to respect the patent rights on Aricept® in the patent's short remaining term. Eisai respectfully requests that the Court grant its motion for a preliminary injunction.

## STATEMENT OF FACTS

### I. Eisai's Invention of Aricept® and the '841 Patent Claiming Aricept®

Alzheimer's disease is a progressive neurodegenerative disease characterized by a steady decline in a patient's cognition, functioning and behavior. (Doody Decl. ¶ 12.)[2] It is the most common form of dementia in the elderly, and today some five million people suffer from the disease. (*Id.*, ¶ 13.)

In the 1980s, no drug was approved by the FDA for the treatment of Alzheimer's disease. Physicians would skip over Alzheimer's disease patients when making hospital rounds with their residents because there was no useful

[2] Eisai has submitted the following declarations in support of its motion: Declaration of Rachelle S. Doody, M.D., Ph.D. ("Doody Decl."); Declaration of Michael R. Pavia, Ph.D. ("Pavia Decl."); Declaration of Yoichi Iimura ("Iimura Decl."); Declaration of Richard A. Kenley, Ph.D. ("Kenley Decl."); Declaration of Richard Killworth ("Killworth Decl."); Declaration of Frank Ciriello ("Ciriello Decl."); Declaration of Henry Grabowski, Ph.D. ("Grabowski Decl."); and Declaration of Hajime Shimizu ("Shimizu Decl."). For the Court's convenience, a brief synopsis of the declarations is attached to this brief as Addendum A.

treatment for the impairment in cognition and memory. There was simply nothing available to help treat the core symptoms of cognitive loss and functional decline. (Doody Decl. ¶ 17.)

By the early 1980s, the literature reported that increasing the level of the neurotransmitter "acetylcholine" in the brain could improve the cognitive function of patients with Alzheimer's disease. (Pavia Decl. ¶ 44.) One theoretical approach to increase acetylcholine in the brain was to selectively inhibit the activity of an enzyme, acetylcholinesterase ("AChE"), which degrades acetylcholine. (*Id.*, ¶¶ 44-45.) A heated race ensued among pharmaceutical companies trying to develop effective cholinergic treatments for Alzheimer's disease. (Iimura Decl. ¶ 14; Pavia Decl. ¶¶ 45, 48-49.)

This work was challenging. The three-dimensional structure of AChE was still unknown. (Pavia Decl. ¶ 47.) And, it was known that increasing the levels of acetylcholine elsewhere in the body outside the brain could cause severe adverse effects, toxicity or even death. (*Id.*, ¶¶ 46, 49, 50, 52; Iimura Decl. ¶ 14.) Indeed, irreversible inhibitors of AChE are deadly chemical weapons (*e.g.*, Sarin and VX). (Kenley Decl. ¶¶ 6, 11-12.) Small changes in structure to a given compound thought to be an AChE inhibitor could cause large and unpredictable changes in effects, including changing the inhibitory activity, effectiveness in

living animals (*in vivo*), selectivity to the brain, bioavailability, and adverse effects or toxicity. (*See* Pavia Decl. ¶¶ 47-53.)

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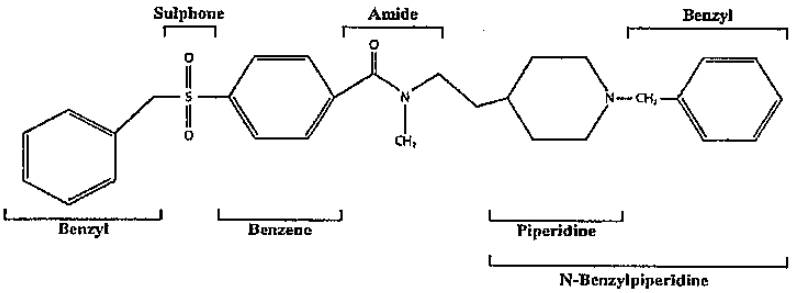
Dr. Rachelle Doody, an expert clinician, was personally involved in failed clinical trials of the AChE inhibiting compound CR-physostigmine, which made patients violently ill. (Doody Decl. ¶ 19.) Another AChE inhibiting compound, metrifonate, had its clinical trials halted because of life-threatening risk of pulmonary paralysis and problems with neuromuscular transmission. (Doody Decl. ¶ 20.)

Dr. Michael Pavia, an expert in medicinal chemistry, was a team leader in Warner-Lambert's development of the AChE inhibiting compound tacrine, the first compound approved by the FDA for treatment of Alzheimer's disease (and the only compound before Aricept®). (Pavia Decl. ¶¶ 6, 7, 49.) Tacrine had liver toxicity problems, short duration of action and the lowest dose was not effective, rendering it a clinical failure. (*Id.*, ¶ 49; Doody Decl. ¶ 21.)

In the 1980s, Eisai was a small pharmaceutical company with no drug products sold in the United States. (Iimura Decl. ¶ 11.) Eisai took on the daunting task of trying to make an effective compound for the treatment of Alzheimer's disease. After years of research, Eisai scientists discovered a compound, "BNAB,"

which showed very strong *in vitro* activity to inhibit AChE and had the following complex structure (*id.*, ¶ 16.)[3]




Eisai filed in Japan and then in the United States a patent application claiming this compound among others. That patent ultimately issued as U.S. Patent No. 4,849,431. (Pavia Decl. ¶¶ 71, 73; Killworth Decl. ¶ 47, 70.)

But, Eisai suffered a major setback when further research in live animals showed that BNAB was easily metabolized and eliminated by the liver before it had a chance to reach the brain. (Iimura Decl. ¶¶ 18-19.) Eisai's scientists were devastated. This failure not only emphasized the unpredictability of these molecules and the huge challenge in developing a successful AChE inhibitor, it underscored the lesson that activity is only one property necessary for a successful drug of this type. (Iimura Decl. ¶ 19.) Eisai's team and its leader, Mr. Hachiro Sugimoto, whose own mother had suffered from dementia, refused to give

[3] Dr. Pavia's declaration explains the concept of *in vitro* inhibitory activity, and also provides a tutorial explaining the complex chemical structures and medicinal chemistry concepts in this case. (Pavia Decl. ¶¶ 15-40, 70 n.2.)

up. (*Id.*, ¶¶ 12, 20.) Eisai agreed to give the scientists another chance. A new project code was assigned – called BNAG. (*Id.*, ¶ 10.)

The story of the discovery of Aricept® during the BNAG project is truly remarkable. The scientist who first synthesized the compound is Dr. Yoichi Iimura. He has submitted a declaration with a detailed account of the discovery. For six months, the scientists worked six days a week, from 8:30 a.m. sometimes until midnight, making and testing compounds, assembling to discuss the results, and making and testing more compounds. (*Id.*, ¶¶ 8, 21-22.) They differed in structure from the BNAB compound all throughout the molecule. (*Id.*, ¶¶ 30.)

During meetings, suggestions would be made, most of which were unsuccessful. (*Id.*, ¶ 23.) Theories for how compounds bound to AChE were also discussed, but that did not result in successful compounds. (*Id.*, ¶¶ 24-25.) The team tested compounds widely varying in structure throughout the molecule, most including an "amide" group on the left-hand side which the team believed was important for activity. (*Id.*, ¶¶ 27, 29, 34, 38, 45, 48, 53.)[4]

At some point during the project, an Eisai researcher noticed a compound with ***poor*** inhibitory activity containing a "ketone" group in its left-hand side, and not an amide group, that Eisai had previously abandoned in the

[4] Dr. Pavia's tutorial depicts and explains an "amide" group. (Pavia Decl. ¶¶ 23.)

BNAB project. (*Id.*, 31.)[5] Using a difficult synthesis method, the Eisai researcher tried modifying the right-hand side of this compound and tested it to see what might happen, given the unpredictability. The compound showed improved *in vitro* activity, but poor effect *in vivo*. (*Id.*, ¶¶ 32-33.) It was not successful.

But, the synthesis challenge piqued the interest of Dr. Iimura, who wanted to find a better synthetic route for carbon-to-carbon bonds in these compounds. (*Id.*, ¶ 35.) Some forty compounds further into the project, Dr. Iimura submitted for testing a second ketone-containing compound with certain differences in the left-hand side structure. Unfortunately, this compound showed poor *in vitro* activity and was unsuccessful. (*Id.*, ¶¶ 36-37.) Another blow to the group, they continued making a variety of different compounds, mostly including "amide" groups. (*Id.*, ¶ 34.)

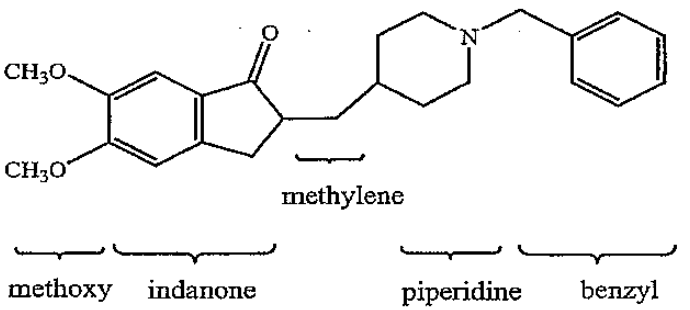
But Dr. Iimura did not surrender. Driven by his personal interest in carbon-to-carbon chemistry, his determination not to give up after the failure of the ketone-containing compound, and observations of internal activity data generated by the Eisai researchers, Dr. Iimura suggested trying an indanone group in the compound. (*Id.*, ¶¶ 39-43.) The first indanone compound created by Dr. Iimura showed inhibitory activity, but was not sufficient under Eisai's screen. (*Id.*, ¶¶ 46-47.) Dr. Iimura later tried modifying certain chemical groups bonded to the

[5] Dr. Pavia's tutorial depicts and explains a "ketone" group. (Pavia Decl. ¶ 21.)

indanone ring, and discovered a compound with good activity both *in vitro* and *in vivo*. But, unfortunately, that indanone compound showed potential liver toxicity. (*Id.*, ¶¶ 50-52.) At that point, the Eisai researchers lost interest in indanone and continued making and testing other structures. (*Id.*, ¶ 53.)

The remainder of the story is classic serendipity. Dr. Iimura was trying to synthesize an amide compound which a fellow scientist had proposed by using a computer modeling program. Dr. Iimura synthesized an indanone compound as a starting material to make the amide-containing compound. Because the synthesis procedure had such a low expected yield, Dr. Iimura made excess of the indanone compound. Having excess and given the lack of predictability, Dr. Iimura submitted for testing both his indanone compound and the amide target compound proposed by the computer modeling. (*Id.*, ¶¶ 59-60.)

Dr. Iimura later learned that the amide compound was unsuccessful, contrary to the computer modeling. But, to his great surprise, the indanone compound had excellent *in vitro* and *in vivo* activity. Dr. Iimura's compound turned out to be donepezil. (*Id.*, ¶¶ 61-62.) The team made more indanone compounds with success, but none was preferred over donepezil. (*Id.*, ¶ 63.) Donepezil has the following structure, explained in Dr. Pavia's declaration (Pavia Decl. ¶ 26):

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Eisai filed in June 1987 a Japanese patent application claiming donepezil and other project compounds, and a U.S. application within a year after. (Killworth Decl. ¶ 71.) The U.S. patent claiming donepezil issued as U.S. Patent No. 4,895,841. (*Id.*, ¶ 90.) The '841 patent prosecution was short (1½ years from filing to issuance). So unique was the molecule Dr. Iimura fortuitously discovered that *donepezil itself was never even rejected over the prior art.* (*Id.*, ¶¶ 71-90.)

## II. Aricept® Has Been Recognized as a Pioneering Discovery

In 1988, Eisai publicly disclosed donepezil at a scientific conference where it generated immediate and surprising excitement among the medicinal chemists who attended. (Iimura Decl. ¶¶ 67-68.) Numerous pharmaceutical companies sought rights in Aricept®. Warner-Lambert, the owner of tacrine,

offered to **REDACTED**

(Exh. 1 at EC 42936-67; Exh. 2 at EC 81022.)[6]

Teva itself wrote Eisai in 1994 stating: "We have noticed with interest that [donepezil] is in mid Phase III Clinical Trials in the U.S. and in Europe. ***For some time we have been looking for an highly selective AChE inhibitor*** which would be an important addition to our new products portfolio." (Exh. 3, TDON 5010247 (emphasis added).) Thus, before this litigation, Teva did not think that it was obvious to find an effective AChE inhibitor.

In 1996, Teva wrote again, stating that, "For some time now we . . . have been following with great interest" the news about donepezil. (Exh. 4 at EC 42023.) Teva stated it had been researching drugs "with the potential for the treatment of Alzheimer's disease," and exclaimed: "All this enables us to spot a winning product – when we see it!" (Exh. 4 at EC 42023.)

Some of the numerous other companies clamoring for rights were: Ciba-Geigy (Exh. 5 at EC 42733; Exh. 6 at EC 83726, 29) **REDACTED**

; Hoffmann-La Roche (Exh. 7 at EC 77485; Exh. 8 at EC 42389; Exh. 9 at EC 42374) **REDACTED**

; Schering Plough (Exh. 10 at EC

[6] "Exh. __" refers to the exhibits attached to the Declaration of Anthony Michael in support of Eisai's motion, submitted herewith.

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SmithKline Beecham (Exh. 11, EC 42116-50); Wellcome Foundation (Exh. 12 at EC 42239); Wyeth-Ayerst (Exh. 13, EC 3618-20); Merck & Co. (Exh. 14, EC 42812); Nippon Roche (Exh. 15, EC 42302); Marion Merrell Dow (Exh. 16, EC 3306; Exh. 17, EC 3300-01); Dupont Merck (Exh. 18 at EC 56442); and Eli Lilly & Co. (Exh. 19 at EC 3292).

After large and expensive clinical trials demonstrating safety and efficacy in humans, in 1996, Eisai submitted its New Drug Application to the FDA. The FDA gave Aricept® "fast-track" review, reserved for drugs that "treat serious illness and fill an unmet medical need." (Exh. 20 at EC 33289; Exh. 21 at EC 4091; Exh. 22 at EC 37724; Exh. 23, website at 1-2.)

In 1997, Aricept® was awarded the Prix Galien special prize, said to be the equivalent of the Nobel prize for pharmaceuticals. (Iimura Decl. ¶ 69.) In 2002, Aricept® was awarded the Emperor's Imperial Invention Prize, the most prestigious prize for invention in Japan. (*Id.*, ¶ 69.)

In 1997, Aricept® was launched in the United States and was an immediate commercial success. Aricept® eradicated the anemic sales of tacrine and effectively created a market for Alzheimer's disease drugs. (Ciriello Decl. ¶ 13.) Currently, Eisai sells over $1.5 billion a year of Aricept® in the United States alone, constituting over 70% of the profits of Eisai Inc. (Ciriello Decl. ¶ 4.) As

only one of the two major drugs sold by Eisai in the U.S., and with its enormous commercial success, Aricept® critically supports the operations of the company. (Ciriello Decl. ¶¶ 4, 14 and 16.)

Numerous generic drug companies have filed ANDAs with Paragraph III certifications respecting the '841 patent, including: Ranbaxy Laboratories, Roxane Laboratories, Apotex, Ivax Pharmaceuticals, Zydus Pharmaceuticals and Par Pharmaceuticals. (*See* Exhs. 24-29.)

## III. Teva's Initial Acquiescence and Ever-Shifting Litigation Positions

Teva has a long history of acquiescence in the '841 patent. Teva admits it knew of the '841 patent since at least

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Between May 2002 and September 2004, Teva had its outside patent counsel study the '841 patent. (Exh. 30, Interrog. Resp. 11; Exh. 34, at 1-2.) In October 2004, Teva filed an ANDA for generic Aricept® -- but with a Paragraph III certification agreeing not to market the drug until ***after*** the patent expired in November 2010. (Exh 35.) Teva thus acquiesced in the strength of the '841 patent, as had numerous other generic competitors.

Teva admits that as of the time it filed its ANDA, and even as late as July 2005, "an opinion of counsel that the '841 patent was invalid, did not exist." (Exh. 30, Interrog. Resp. 11; Exh. 36, Tr. at 37, lines 7-11.) Teva's outside patent counsel, after two years of study, could not find a basis to attack the '841 patent.

In July 2005, Eisai met with Teva at Teva's outside counsel's office. During that meeting, Teva asked for rights to sell Aricept®. (Shimizu Decl. ¶¶ 3-4.) Teva tried to pressure Eisai saying that, if Eisai would cooperate, Teva would consider holding off filing a challenge to the Aricept® compound patent and would withdraw its pending challenge to Eisai's other major drug, Aciphex® (rabeprazole).[7] (Shimizu Decl. ¶ 4.) Teva thus threatened Eisai's patent at a time when it had no opinion of invalidity. After Eisai declined, in October 2005, Teva suddenly obtained an opinion of counsel and amended its ANDA to include, for the first time, a validity challenge to the '841 patent. (Exh. 30, Interrog. Resps. 11-12; Exh. 38.)

Teva's October 2005 patent certification had a baseless obviousness challenge -- combining half a molecule from a patent on anti-depressants with half a molecule from a patent on dopamine antagonists and arguing the resulting

[7] Teva's rabeprazole challenge at that time was being litigated in the Southern District of New York. *Eisai v. Teva*, Civ. Action Nos. 03-9053, -9223 (S.D.N.Y.) (GEL). Teva has represented to this Court that it has no documents pertaining to the July 2005 meeting. (Exh. 37, Teva Opposition to Motion to Compel, at 4.)

mongrel molecule would be an effective AChE inhibitor for treating Alzheimer's disease. (Exh. 38.)

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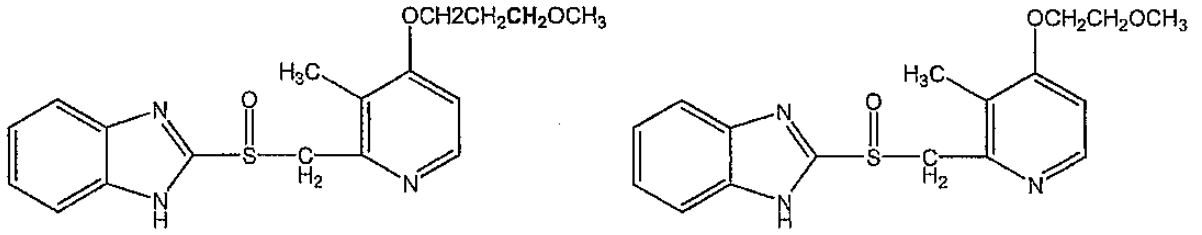
(Exh. 39, Interrog. Resp. 2.) Then, in December 2006, Teva simply changed its obviousness theory -- asserting a frivolous hindsight pathway to donepezil by combining ***seven*** different references in view of ***seventeen*** other references. (Exh. 40, Interrog. Resp. 2, pp. 2-4.) In December 2007, Teva changed positions yet again and filed an amended complaint completely withdrawing its obviousness defense, conceding (under the excuse of "streamlining the action" for trial) that the '841 patent "satisf[ies] the requirements for patentability." (Exh. 41, Corrected Amended Answer, ¶ 24.)

Teva has known of the '431 patent and Paragamian (U.S. Patent No. 3,476,759) since at least March 14, 2006, having identified them in its initial disclosures. (Exh. 42 at 3.) Teva has known of Kenley since at least December 21, 2006, citing it in an interrogatory response. (Exh. 40 at 7.) Yet, throughout this litigation, Teva has never even tried to argue that the '841 patent claims are invalid for double-patenting based on these three references. (*See* Exh. 40.)

On May 11, 2007, the district court ruled against Teva in the Aciphex® lawsuit, giving the parties an advance copy of its opinion, *Eisai v. Teva*, 2007 WL 1437834 (S.D.N.Y. 2007). The court rejected Teva's argument that Eisai committed inequitable conduct by not disclosing one of its co-pending patent

applications. The court found that Teva had failed to prove that the patent office would likely have issued an obviousness type double patenting rejection of the two compounds depicted below, which differ merely by the presence of a single methylene ($CH_2$) group within one of the substituents on the molecule:




The district court stated that Teva had failed to prove "a factual, prior-art based path by which [the patented compound] and [the compound of the co-pending application] would have been deemed by the PTO to be *prima facie* obvious over one another – and, thus, patentably indistinct – offering only conclusory or unpersuasive expert testimony to that end." *Eisai v. Teva*, 2007 WL 1437834, at *21.

Two business days later, on May 15, 2007, Teva moved to amend its complaint in this case to add, for the first time, an allegation of inequitable conduct. Applying the liberal standards for amendment of pleadings, on December 6, 2007, Magistrate Judge Salas allowed Teva to amend. (D.I. 102 (allowing one allegation pled with particularity); D.I. 133 (striking Teva's subsequent amended pleading because it exceeded the prior grant of the motion to amend).)

Unfazed by the Southern District of New York's ruling in Aciphex®, Teva once again argues that Eisai committed inequitable conduct by not disclosing a co-pending application. Teva's argument this time is far less likely to succeed than the defense it lost in the Aciphex® litigation. Here, the difference between the compounds is not just a single methylene group on a substituent – but rather an entirely different left-hand side of the basic core structure of the compound, occurring in a technical field that was challenging, very complex and highly unpredictable. (*See* Pavia Decl. ¶¶ 62-63, 66-76.)

## ARGUMENT

### I. LEGAL STANDARD FOR THE GRANT OF A PRELIMINARY INJUNCTION

The standards applied to a request for a preliminary injunction are "no more nor less stringent in patent cases than in other areas of the law." *H.H. Robertson Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 387 (Fed. Cir. 1987). When determining whether injunctive relief should be granted, the courts consider four factors in their analysis:

> (1) whether the movant has shown a reasonable probability of success on the merits;
>
> (2) whether the movant will be irreparably harmed by denial of the injunctive relief sought;
>
> (3) whether the threatened injury to the movant if an injunction is not granted outweighs the threatened harm to the non-movant if the injunction is granted;

(4) the impact of a preliminary injunction on the public interest.

*Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1363 (Fed. Cir. 2001.) The "court must balance these four factors, as their relative weights warrant, in service to the interest of justice." *Monsanto Co. v. McFarling*, 302 F.3d 1291, 1297 (Fed. Cir. 2002).

## II. EISAI HAS SHOWN A LIKELIHOOD OF SUCCESS ON THE MERITS

### A. Legal Standards for Demonstrating Likely Success

A preliminary injunction is determined "in the context of the presumptions and burdens that would inhere at trial on the merits." *H.H. Robertson*, 820 F.2d at 388. The patent owner must, consistent with those burdens of proof, show that its infringement claim will likely withstand the defendant's challenge to patent validity. *See Purdue Pharma*, 237 F.3d at 1363. The patent owner demonstrates likely success if -- taking into account the underlying burden of proof on the defendant -- either (1) the defendant fails to raise a "substantial" question of validity, or (2) even if the defendant does raise a "substantial" question, the patent owner shows that the defense "lacks substantial merit." *Id.*

"The grant of a preliminary injunction does not require that infringement be proved beyond all question, or that there be no evidence supporting the viewpoint of the accused infringer." *H.H. Robertson*, 820 F.2d at 390.

The '841 patent is presumed to be enforceable, and the presumption exists at every stage of the litigation. 35 U.S.C. § 282; *Canon Computer Sys., Inc. v. Nu-Kote Int'l Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998). A defendant challenging the patent has the heavy burden of proving unenforceability by clear and convincing evidence. *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 872 (Fed. Cir. 1988) (*en banc*). Under the heavy "clear and convincing" standard, the proof must "place in the ultimate fact finder an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Zeller Plastik, Koeh, Grabner & Co. v. Joyce Molding Corp.*, 698 F. Supp. 1204, 1220 (D.N.J. 1988) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

Teva's sole surviving defense is a charge of inequitable conduct. "Inequitable conduct resides in a failure to disclose material information, or the submission of false material information, with an intent to deceive, and those two elements, materiality and intent, must be proven by clear and convincing evidence." *Kingsdown*, 863 F.2d at 872, 876 (overruling language in prior cases to make clear that even gross negligence is not in itself sufficient for inequitable conduct).

Information is "material" where "there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." *Pro-Mold & Tool*

*Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1575 (Fed. Cir. 1996); 37 C.F.R. § 1.56 (1987).

Proving intent to deceive means more than proving that the applicant intended to do what he did in patent prosecution; "it means that the inventor intended to deceive or mislead the examiner into granting the patent." *Therma-Tru Corp. v. Peachtree Doors Inc.*, 44 F.3d 988, 995 (Fed. Cir. 1995); *Dayco Prods., Inc. v. Total Containment Inc.*, 329 F.3d 1358, 1367 (Fed. Cir. 2003) ("inequitable conduct requires not intent to withhold, but intent to deceive").

"The defense of inequitable conduct is frequently invoked in patent infringement cases, and is likewise frequently abused." *Intelli-Check, Inc. v. Tricom Card Techs., Inc.*, 2005 U.S. Dist. LEXIS 38794, *16-17 (D.N.J. Nov. 10, 2005). The Federal Circuit has characterized the defense as: an "absolute plague," *Burlington Indus., Inc. v. Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988); a "much abused and too often last-resort allegation," *Preemption Devices, Inc. v. Minnesota Mining & Mfg. Co.*, 732 F.2d 903, 908 (Fed. Cir. 1984); and an overplayed defense "cluttering up the patent system," *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1454 (Fed. Cir. 1984). It was to "mitigate the 'plague' whereby every patentee's imperfections were promoted to 'inequitable conduct' that [the Federal Circuit] reaffirmed that both materiality and culpable

intent must be established." *Allied Colloids Inc. v. American Cyanamid Co.*, 64 F.3d 1570, 1578 (Fed. Cir. 1995).

**B. Teva's Materiality Arguments Are Devoid of Merit**

Teva asserts that the '431 patent was material to the prosecution of the '841 patent application because Claims 1-4 and 7 of the '841 patent "likely would have been subject to a non-provisional obviousness-type double patenting rejection in view of the '431 patent, the '759 patent [Paragamian] and Kenley." (Exh. 43 Amended Answer ¶ 34; Exh. 44 at 6.) Teva relies on the compounds of Claims 1, 4 and/or 12 of the '431 patent. (Exh. 44 at 18-19.)

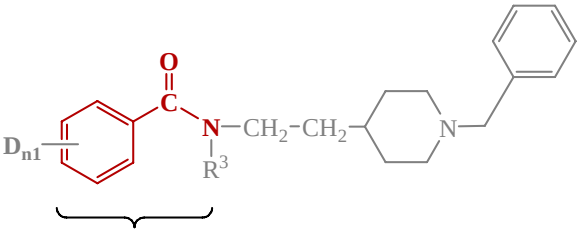
"The double patenting doctrine generally prevents a patentee from receiving two patents for the same invention." *Bayer A.G. v. Dr. Reddy's Labs., Ltd.*, 518 F. Supp. 2d 617, 638 (D. Del. 2007). Obviousness type double patenting is a judicially created doctrine "adopted to prevent claims in separate applications or patents that . . . claim inventions so alike that granting both exclusive rights would effectually extend the right of patent protection." *In re Metoprolol Succinate Patent Litigation*, 494 F.3d 1011, 1016 (Fed. Cir. 2007).

Teva does not and cannot argue that the structures claimed in the '431 patent are effectively the same as (*i.e.*, "patentably indistinct" from) the structures claimed in the '841 patent. (*See* Exh. 44 at 23, ¶ j.) Clearly, they are different. In his declaration, Dr. Pavia depicts the claims of the '431 and '841 patents at issue,

and compares the claims to show how the entire left-hand sides of the core structures are different. (Pavia Decl. ¶¶ 63, 66-68.)

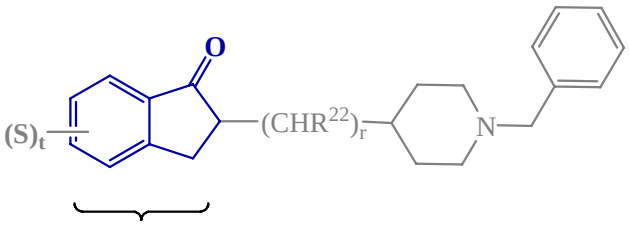
For example, Claim 12 of the ’431 patent recites compounds having a left side with a straight-chain benzamide group. (Pavia Decl. ¶ 67.) In contrast, every claim of the ’841 patent requires an indanone group in the left-hand side, which is a different structure composed of two rings fused together with the five-membered ring bonded to an oxygen atom. (*See id.*, ¶¶ 63, 68.) The different structures are depicted below:

’431 Patent Claim 12




**Straight Chain Benzamide**

’841 Patent Claim 4




**Indanone**

Teva points out that the right-hand sides of the molecules are the same. While true, this is irrelevant in the context of these complex compounds. As Dr. Pavia (who has direct industry experience at the time of the invention in this technical field) and Mr. Killworth (an expert in patent office practice and procedure) explain in their declarations, medicinal chemists and patent examiners understand that an entire molecule must be considered when considering distinctness of chemical structures, particularly where, as here, there are significant

differences in half of the core structure of the molecule. (Pavia Decl. ¶¶ 66, 69-76; Killworth Decl. ¶ 94.)

Eisai experienced this scientific fact in its research, where compounds having the same right-hand sides as the '431 patent claims often had dramatically different and unpredictable properties depending on the remainder of the structure. (*E.g.*, Iimura Decl. ¶¶ 17-19, 31, 33-34, 36-37; Pavia Decl. ¶¶ 70-71, 117.)

As discussed above, the difference between the '431 and '841 patent claims are far more dramatic than those found to be patentably distinct by the Southern District of New York in *Eisai v. Teva*, 2007 WL 1437834, at *21. They are also more dramatic than those found by the Federal Circuit to be patentably distinct in *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 943 (Fed. Cir. 1992). In *Ortho*, two molecules that differed by the location of double bonds in the ring structures were held patentably distinct. *Ortho*, 959 F.2d at 939, 943, 947 ("gon-4-ene" is patentably distinct from a prior claim to a "gon-5(6)-ene" or "gon-5(10)-ene"). The differences here are also more dramatic than in *Bayer A.G. v. Dr. Reddy's Labs., Ltd.*, where the court found two structures patentably distinct that differed only by the presence of a methoxy group ($OCH_3$) versus a fluorine (F) or chlorine (Cl) atom at one position on the molecule. 518 F. Supp. 2d at 641.

The prosecution histories of the '431 and '841 patents confirm the respective structures are patentably distinct. As shown in Mr. Killworth's

declaration, the PTO issued a "restriction requirement" in the '431 patent prosecution finding that compounds in this technical field with different structures on the left-hand side were patentably distinct from one another, notwithstanding that the right-hand sides were identical. (Killworth Decl. ¶¶ 31-39, 55-64.) In the '841 patent prosecution, the examiner issued a "restriction requirement" asserting that the indanone group in the '841 patent claims rendered those compounds patentably distinct from structures lacking that group. (*Id.*, ¶¶ 75-83.) These restriction requirements confirm that no reasonable examiner would consider the '431 and '841 patent claims to be indistinct. (*Id.*, ¶¶ 32-33, 95-98.)

Resorting again to hindsight, Teva argues that the '841 claimed compounds are "obvious variants" of the '431 claimed compounds because one of ordinary skill would combine a piece of the '431 structure with a piece of a structure in Paragamian, based on Kenley, and reasonably expect the resulting combination to be an effective AChE inhibitor. (Exh. 44 at 6-9, 23; Pavia Decl. ¶ 64.) Every aspect of this argument is fundamentally flawed. (Pavia Decl. ¶¶ 64-123; Kenley Decl. ¶¶ 21-38.)

At the outset, the Paragamian compounds are merely intermediates used to synthesize a hypotensive agent. (Killworth Dec. ¶¶ 102-104.) Under Federal Circuit law, a reasonable examiner would not combine a piece of the '431 patent compounds with a piece of an intermediate from Paragamian used to make a

structure having a totally different function. (*See* Killworth Decl. ¶¶ 105-113.) *See also In re Lalu*, 747 F.2d 703, 707 (Fed. Cir. 1984); MPEP § 2144.09 (copy at Killworth Decl. Exh. 28). Nor is there any reason in science or logic to do so. (Pavia Decl. ¶¶ 109-111.)

But even if Teva could get past this insurmountable hurdle, Teva's dependence on Kenley fails because (a) Kenley does not teach what Teva says it does; and (b) even if it did, the teaching is so general that it would not make a particular compound obvious. In addition to the declaration of Dr. Pavia, Eisai has submitted a declaration by Dr. Kenley himself who shows that Teva is misstating his article.

Dr. Pavia and Dr. Kenley show in their declarations that the Kenley article does not teach one of ordinary skill that increasing hydrophobicity of a piece of the molecule will reliably predict an increase in activity (again confirmed by Eisai's own experience), as Teva asserts. (Pavia Decl. ¶¶ 83-96, 99; Kenley Decl. ¶¶ 21-31.) Dr. Pavia and Dr. Kenley also show that, even if Kenley did provide such a generalized teaching, there would still be an endless number of possible structures to make with unpredictable properties. (Pavia Decl. ¶¶ 105-106, 113-116; Kenley Decl. ¶¶ 34-36.) Teva uses impermissible hindsight to assert that one of skill would obviously change the left side of the '431 claimed structures to indanone, with a reasonable expectation that the resulting structure would be

effective at inhibiting AChE. (Pavia Decl. ¶¶ 105-106, 113-123; Kenley Decl. ¶¶ 37-38.) *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (success was finding a compound that had high activity, few side effects and lacked toxicity; generic company's proposed manipulations of prior compounds had all the earmarks of somebody applying hindsight).

Teva knew about the '431 patent, Paragamian and Kenley since at least December 2006 and never even tried to argue that the '841 patent was invalid for double patenting. (*See* page 18, above.) If a three-way combination of the '431 patent claims, Kenley and Paragamian really made obvious the '841 claimed structures, then Teva surely would have asserted double patenting invalidity the moment it saw these references. Teva's failure to do so belies its arguments now about their importance.

In sum, Eisai has demonstrated more than a reasonable probability it will succeed in withstanding Teva's assertion of materiality. No reasonable examiner would consider the '431 patent and the '841 patent claimed structures to constitute obviousness type double patenting of effectively the same compounds.

### C. Teva Will Not Prove Intent To Deceive

Materiality is only half of Teva's burden. Teva will not prove intent to deceive either. Teva's intent theory is that Eisai concealed the information about the '431 patent and Kenley to prevent the examiner from rejecting Claims 1-

4 and 7 of the '841 patent for double patenting. (Exh. 44 at 14.) But donepezil was specifically claimed in Claim 8 of the '841 patent. (Pavia Decl. ¶ 28.) Teva does not even assert that Claim 8 would have been rejected. (Exh. 44 at 18-19.)

So, Teva wants the Court to believe that Eisai engaged in a scheme of fraud potentially fatal to its patent to hide information that was not even material to the patentability of the compound Eisai cared about -- donepezil. This does not make sense.

In most inequitable conduct cases, the defendant tries to show that one or two individuals had a real intent to deceive. Not Teva in this case. Teva asserts that the following persons intended to deceive the PTO:

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If Teva is to be believed, Eisai engaged in a worldwide scheme of fraud to conceal information that was not even material to donepezil. Teva's allegations are implausible.

In particular, Teva says that **REDACTED** were allegedly aware of Kenley's significance in teaching a "two-site"

binding theory;[8] they knew from Kenley that a more hydrophobic "terminal fragment" would result in relatively stronger effective inhibition of the enzyme; and they used the teaching from Kenley to quickly arrive at the indanone compound. (Exh. 44 at 13-14.)

First of all, this is fiction. Dr. Iimura synthesized the first compound containing an indanone in its left-hand side, not REDACTED Teva knows this because they deposed Dr. Iimura. And, Dr. Iimura did not create the indanone compound because Kenley supposedly taught that increasing hydrophobicity of a terminal fragment will likely result in more effective inhibition, which Kenley does not teach anyway. (Iimura Decl. ¶¶ 31-43, 70-73; Kenley ¶¶ 21-31; Pavia ¶¶ 83-96.) Dr. Iimura did not even see Kenley before he synthesized these molecules. (Iimura Decl. ¶ 71.) Finally, the indanone compound was not, as Teva says, made quickly after the June 16, 1986 meeting -- Eisai made and tested over a hundred more compounds before Dr. Iimura tested the first indanone compound. (Iimura Decl. ¶¶ 24-46.)

Second, even if REDACTED thought Kenley's reference to "two-site" binding meant that changing the left-side of the compound to a different structure with a higher hydrophobicity would result in greater

[8] A "two-site" binding theory refers to a very general theory that AChE has two "regions" (anionic and hydrophobic) where AChE binds to ACh. (Pavia Decl. ¶¶ 89-91; Kenley ¶¶ 22-27.)

inhibitory activity, this still does not prove that they thought Kenley made the '841 patent claimed compounds obvious variations of compounds claimed in the '431 patent. A teaching to increase hydrophobicity of a part of a molecule is so general as to allow an infinite number of possible changes. (Pavia Decl. ¶¶ 105-106; 113-116; Kenley Decl. ¶¶ 36.) And, Teva does not and cannot even allege that Kenley provides predictability for *in vivo* effects of those changes, such as selectivity to the brain, side effects, toxicity, and ability to resist metabolism (*i.e.*, a fundamental problem with the BNAB compound). (Exh. 44 at 7-9; Pavia Decl. ¶¶ 80-81.) Intent to deceive may not be found just because an inventor knew of the existence of a reference. *Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 694 (Fed. Cir. 2001). And the Federal Circuit has condemned arguments of intent, like Teva's here, asserting an "inference on an inference on an inference." *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1417 (Fed. Cir. 1987).

Teva does not accuse Dr. Iimura of intent to deceive. (Exh. 44 at 13.) So, in effect, Teva accuses certain inventors of failing to disclose Kenley for the alleged teaching it provided to synthesize an indanone-containing compound -- even though these inventors did not first make such a compound. On the other hand, the person who did first think to synthesize a compound containing an indanone, Dr. Iimura, is not accused of inequitable conduct because he never looked at Kenley! Teva's assertions make no sense.

Teva accuses Mr. Taniguchi and Eisai's U.S. lawyers of having intent to deceive, but there is no evidence they even knew of Kenley. Further, nothing about the '431 patent contradicts what Eisai's attorney truthfully said during the brief '841 patent prosecution about the structure of Paragamian's intermediates used to make hypotensive agents. (*See* Killworth Decl. ¶¶ 114-115.)

The simple fact is that the '841 and '431 patents claim very different and patentably distinct compounds. The Manual of Patent Examining Procedure makes clear there is no duty to disclose co-pending applications with patentably distinct claims. (Killworth Decl. ¶ 98, citing MPEP § 2001.06(b).) The Code of Federal Regulations made clear that there was no duty to disclose information which is not material. (*Id.*, citing 37 C.F.R. § 1.56 and MPEP § 2001.) There is no evidence that anyone believed, or should have believed, that the '431 patent claims were important to a reasonable examiner's decision whether to allow the '841 patent application to issue as a patent. Teva will not succeed in proving intent to deceive by clear and convincing evidence.

**D. Additional Factors Support Likely Success**

In addition to materiality and intent, which Teva will not succeed in proving, Teva also must demonstrate that the equities on balance warrant rendering the '841 patent unenforceable. *Kemin Foods, L.C. v. Pigmentos Vegatales del Centro, S.A. de C.V.*, 464 F.3d 1339, 1346 (Fed. Cir. 2006). Teva cannot make

that showing either. Here, the '841 patent claims represent an important compound in the treatment of Alzheimer's disease. (Doody Decl. ¶¶ 9, 22-33.) The patent is admittedly valid and infringed. (*See* page 3, above.) Indeed, this is an unusual case in that numerous generic drug companies have acquiesced in the '841 patent by filing Paragraph III certifications. (*See* page 16, above.) Teva also acquiesced in the '841 patent for many years. (*See* pages 16-17, above.) *See Forest Labs., Inc. v. IVAX Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006) (a Paragraph III certification reflects acquiescence in the patent). In addition, a myriad of innovator pharmaceutical companies expressed their faith in Aricept®. (*See* pages 14-15, above.)

Teva is not deserving of a ruling rendering the '841 patent unenforceable, so Teva can take over the huge market for donepezil existing because of the significance of the invention of the '841 patent. *See Eisai v. Teva*, 2007 WL 1437834, at *31 (finding that equity did not warrant holding Eisai's valid patent unenforceable).

## III. EISAI WILL SUFFER IRREPARABLE HARM UNLESS TEVA IS ENJOINED

"[B]ecause the principal value of a patent is its statutory right to exclude, the nature of the patent grant weighs against holding that monetary damages will always suffice to make the patentee whole." *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1456-57 (Fed. Cir. 1988). Both the Federal Circuit and this

Court have "consistently held that a district court should presume that a patent owner will be irreparably harmed when, as here, a patent owner establishes a strong showing of likely infringement of a valid and enforceable patent." *See, e.g., Pfizer, Inc. v. Teva Pharms., USA, Inc.*, 429 F.3d 1364, 1381 (Fed. Cir. 2005).[9] Because Eisai has made a strong showing of likely success on the merits, there is a presumption of irreparable harm.[10]

Eisai has further demonstrated actual irreparable harm. Unlike many pharmaceutical companies, and indeed unlike Teva itself, Eisai's revenues depend on the two major products it sells in the U.S. -- Aricept® and Aciphex®. (Ciriello Decl. ¶ 4.) U.S. sales of its blockbuster drug Aricept® are responsible for 70% of Eisai Inc.'s profits and a quarter of Eisai Co., Ltd.'s revenues worldwide, and sales of Aricept® continue to grow. (*Id.* ¶ 16.) Eisai has only a little over two years left until the '841 patent expires to use those revenues to sustain its continued

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[9] *See also Purdue Pharma*, 237 F.3d at 1367-68; *Ortho-McNeil Pharm., Inc. v. Mylan Labs. Inc.*, Civ. A. Nos. 04-1689 and 06-757, 2006 WL 3019689, at *10 (D.N.J. Oct. 23, 2006).

[10] Teva has elsewhere argued that the presumption of irreparable harm does not apply after *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 126 S. Ct. 1837 (2006). But *eBay* has not overruled binding Federal Circuit precedent establishing the presumption. *eBay* held that a court must exercise discretion consistent with principles of equity in determining whether to grant permanent injunctive relief. *Id.* at 1841. A district court still applies equitable discretion when recognizing a rebuttable presumption of irreparable harm in the course of determining whether to grant a preliminary injunction.

operations. *See Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1247 (Fed. Cir. 1989) (reversing the district court's refusal to issue an injunction, due in part to irreparable harm resulting from the fact that the patent in question would expire in less than four years).[11]

Eisai has organized its operations and future business plans in reliance on patent exclusivity through the November 2010 expiration of the '841 patent. (Ciriello Decl. ¶¶ 37-42.) It is undisputed that an at-risk launch by Teva will result in a sudden and drastic reduction in Aricept®'s revenues and market share, exacerbated by the concentrated prescribing practices used for Aricept®. (*Id.*, ¶¶ 18, 21; Grabowski Decl. ¶¶ 19-21.) Teva's own documents predict that a generic launch will result in

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Teva will likely flood the market with generic donepezil, thus reducing the demand for Aricept® for the entire remaining patent term. (*Id.*, ¶¶ 25-26; Ciriello Decl. ¶ 22.)

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[11] *See Pharmacia & Upjohn Co. v Ranbaxy Pharms., Inc.*, 274 F. Supp. 2d 597, 614 (D.N.J. 2003) ("the remaining relatively short life of the patent" weighs in favor of a finding of irreparable harm), *aff'd in relevant part*, 85 Fed. Appx. 205, 214-15 (Fed. Cir. 2003) (affirming district court's reliance on loss of short remaining life of the patent); *Quantronix, Inc. v. Data Trak Techs., Inc.*, 503 F. Supp. 2d 1152, 1163 (D. Minn. 2007) ("the fact that the [patent at issue] will expire in approximately two years" supports granting preliminary injunction).

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These harms cannot be adequately compensated by a damages award. *See Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368, 1382-83 (Fed. Cir. 2006) (affirming trial court's ruling that the potential reduction of plaintiff's work force and loss of goodwill constituted irreparable harm warranting a preliminary injunction); *Abbott Labs. v. Sandoz, Inc.*, 500 F. Supp. 2d 846, 854 (N.D. Ill. 2007) (harm caused by lost sales representatives and lost goodwill cannot be fully remedied by money).

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An at-risk generic launch of Aricept® will require Eisai to terminate or postpone many of them. This loss of business opportunity is irreparable. *Sanofi-Synthelabo*, 470 F.3d at 1382-83 (discontinuation of clinical trials is an irreparable harm supporting a preliminary injunction); *Bio-Technology Gen. Corp. v. Genentech Corp.*, 80 F.3d 1553, 1565-66 (Fed. Cir. 1996) (being forced to reduce a party's research and development activities supports a finding of

irreparable harm); *Pharmacia & Upjohn Co.*, 274 F. Supp. 2d at 614 (irreparable harm includes "loss of current research opportunities resulting from loss of funding"), *aff'd in relevant part*, 85 Fed. Appx. at 214-15.[12]

Because of Aricept®'s enormous commercial success and Eisai's heavy dependence on the revenues from its sales, Eisai cannot take business counter-measures against a generic launch that would avoid irreparable harm. Eisai's future depends on its ability to continue to use the revenues generated by its blockbuster drug now through the remainder of the patent term. (*See, e.g.*, Ciriello Decl. ¶¶ 37, 41-42, 47.)

## IV. THE BALANCE OF HARDSHIPS AND PUBLIC INTEREST FAVOR PLAINTIFFS

Teva is a diversified company which currently has some 150 ANDAs pending for generic versions of products having approximately $88 billion in sales. (Grabowski Decl., Ex. 8.) Teva should not be heard to claim it cannot wait to start selling generic Aricept®, having delayed for years and originally filing a Paragraph III certification agreeing to wait until the patent expired. (*See* pages 16-

[12] Eisai is not seeking to compel a finding of irreparable harm by simply making a generalized statement of lost research opportunity, which the Federal Circuit and this Court have recognized as insufficient in other cases. *Novartis Corp. v. Teva Pharms. USA, Inc.*, 2007 WL 1695689, at *28 (D.N.J. 2007) (quoting *Eli Lilly & Co. v. Am. Cyanamid Co.*, 82 F.3d 1568, 1578 (Fed. Cir. 1996)). Rather, Aricept® is one of the two major products sold by Eisai in the US with blockbuster and growing sales, making it of critical importance to Eisai's continued operations in the remaining patent term. (Ciriello Decl. ¶¶ 4, 14 and 16.)

17, above.) By contrast, Eisai's future depends on its ability to retain sales from its blockbuster drug Aricept® as a source of funding for the remainder of the patent term.

The greater importance of the patented product to Eisai over Teva is properly considered when balancing the hardships of the parties. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, Civ. A. Nos. 04-1689, 06-757, 2006 WL 3019689, at *10 (D.N.J. Oct. 23, 2006) (without the preliminary injunction, plaintiff "stands to only lose the value of its patent" while defendant "would only lose the ability to go on to the market and begin earning profits earlier"); *see, e.g., Garvey Corp. v. Barry-Wehmiller Design Group*, 365 F. Supp. 2d 893, 900 (N.D. Ill. 2005) (balance of hardships favored plaintiff where defendant manufactured more than one product and would not be devastated by a preliminary injunction).

The public interest is served by the issuance of a preliminary injunction in this case. Drug discovery is a high risk business, with far more failures than successes. (Grabowski Decl. ¶ 41; Pavia Decl. ¶ 29-33.) Aricept® was one of those success stories -- a significant contribution to medicine. (Doody Decl. ¶ 9, 10, 22-33.) Without the '841 patent and Eisai's investment into the discovery of Aricept®, Teva would not ever have had the opportunity to sell a generic version of donepezil. The public needs to have confidence that a basic compound patent protecting an important drug discovery will receive protection by

the courts. "It is in the public interest to protect the pharmaceutical industry's investment into the discovery of new drugs." *Ortho Pharm. Corp. v. Smith*, 15 U.S.P.Q.2d 1856, 1863 (E.D. Pa. 1990); *see also Pfizer*, 429 F.3d at 1382.

## CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that Teva be enjoined.

February 15, 2008

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## Addendum

The following are synopses of the declarations of the experts and of Eisai's employees which have been filed in support of this motion.

### A. Yoichi Iimura, Ph.D.

Dr. Yoichi Iimura is an inventor of the '841 patent. Dr. Iimura was the first inventor in Eisai's research project to synthesize a compound including an indanone structure. Dr. Iimura describes the remarkable story of the invention of Aricept® and the compounds claimed in the '841 patent, including the unpredictability of the work, the real-world difficulties that the inventors faced in trying to make an effective AChE inhibitor, and the numerous failures of the team. Dr. Iimura further shows how Teva's arguments about the Kenley article are unrealistic in light of the work actually done by the Eisai inventors.

### B. Michael Pavia, Ph.D.

Dr. Michael Pavia is an expert in medicinal chemistry with direct experience at a pharmaceutical company in the relevant time period in the field of compounds for use in the treatment of Alzheimer's disease. After earning his Ph.D. in Organic Chemistry from The University of Pennsylvania, Dr. Pavia went to work for Warner-Lambert Company where he carried out extensive work in researching drugs for the treatment of Alzheimer's disease, including AChE inhibitors, acetylcholine agonists and neuropeptide approaches to the disease. Dr. Pavia was a member of the central nervous system leadership team at Warner-Lambert during the development of tacrine, the first compound approved by the FDA for the treatment of Alzheimer's disease. Dr. Pavia provides the Court with a tutorial on aspects of medicinal chemistry necessary to understand the issues in this case. Dr. Pavia then provides a showing in detail of why Teva's assertions of "obvious variation" lack merit from the perspective of one of ordinary skill in the art in the relevant time frame.

### C. Richard A. Kenley, Ph.D.

Dr. Richard Kenley is an expert in medicinal chemistry and the author of the Kenley article cited by Teva as support for its inequitable conduct argument. Dr. Kenley provides a tutorial with regard to the technological aspects of his article. Dr. Kenley shows that his article does not contain the teachings Teva argues it does, and that the article would not be used by one of ordinary skill in the art to make Teva's proposed changes or reliably predict that they would result in an effective AChE inhibitor.

### D. Richard Killworth

Richard Killworth is an expert in patent office practice and procedure. Mr. Killworth explains the prosecution history of the '841 patent. Mr. Killworth also explains the prosecution history of the '431 patent, relied upon by Teva. Mr. Killworth shows that no reasonable examiner would consider the claimed structures of the '431 and '841 patent to be patentably indistinct, particularly in light of the restriction requirements occurring in the patent prosecution histories. Mr. Killworth further shows that no reasonable examiner would combine a portion of the structure of the '431 patent claims with a portion of a compound used in Paragamian merely as an intermediate to make a compound with a totally different property, as Teva asserts would be necessary for an obviousness type double patenting rejection.

### E. Rachelle Doody, M.D.

Dr. Rachelle Doody is a practicing neurologist, professor of neurology, and the leader of the Alzheimer's disease research program at Baylor College of Medicine. Dr. Doody has been a principal investigator in over 35 clinical studies concerning Alzheimer's disease and has 21 years of clinical experience in the field. Dr. Doody explains Alzheimer's disease and the clinical importance of Aricept®. Dr. Doody contrasts the clinical success of Aricept® with the failures of AChE inhibiting compounds such as tacrine, CR-physostigmine and metrifonate.

### F. Frank Ciriello

Frank Ciriello is Eisai Inc.'s Senior Vice President of its Specialty and Primary Care Business Unit. Mr. Ciriello is responsible for managing the marketing, sales, managed care markets, co-promotion relationships and medical affairs relating to Eisai's mainstay products, Aricept® and Aciphex®. He describes the critical importance to Eisai of Aricept®, which constitutes approximately 70% of Eisai Inc.'s profits and a quarter of Eisai Co., Ltd.'s worldwide revenues.

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### G. Henry Grabowski, Ph.D.

Dr. Henry Grabowski is a Professor of Economics and the Director of the Program in Pharmaceuticals and Health Economics at Duke University. Dr. Grabowski has extensively studied the economics of the pharmaceutical industry, and teaches a graduate course at Duke on economics and policy issues in that industry. Dr. Grabowski explains that Teva's at-risk launch of a generic donepezil product would irreparably harm Eisai because of unique circumstances arising from Eisai's dependence on Aricept® through the short remaining life of the patent. Dr. Grabowski further explains that the impact of such a launch upon Eisai is significantly more harmful than an injunction would be on Teva, because Teva is a highly diversified company that is not reliant upon sales of generic donepezil.

### H. Hajime Shimizu

Hajime Shimizu is the Chairman & CEO of Plaintiff Eisai Inc. Mr. Shimizu also serves as the Senior Vice President of the Pharmaceutical Business, United States, for Plaintiff Eisai Co., Ltd. Mr. Shimizu recounts the meeting between Eisai and Teva that occurred in July 2005, at Teva's request in the offices of Teva's outside counsel.